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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/659,643	09/12/2000	James J. Gibbons Jr.	AM100081	6975

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EXAMINER	
ROYDS, LESLIE A	
ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/659,643	GIBBONS JR. ET AL.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 15-18 are presented for examination.

The present application has been revived from unintentional abandonment pursuant to the petition decision of October 2, 2006 issued in response to the petition filed June 16, 2006.

A request for continued examination under 37 C.F.R. 1.114, including the fee set forth in 37 C.F.R. 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R. 1.114, and the fee set forth in 37 C.F.R. 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 C.F.R. 1.114. Applicant's payment and submissions filed June 16, 2006 have been received and entered into the present application. Accordingly, the submissions of June 16, 2006 have each been entered into the present application and prosecution has been reopened.

Claims 15-18 are newly added, pending and under examination. Claims 1, 3 and 5-7 have been cancelled.

Applicant's arguments, filed June 16, 2006, have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Objections to the Claims (New Grounds of Objection)

Claims 17 and 18 are objected to for misspelling the word ---paclitaxel--- as "paclitaxcel" at line 2 of each of the claims. Appropriate correction is required.

Claim Rejections - 35 USC § 112, First Paragraph, Scope of Enablement (New Grounds of Rejection)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating non-small cell lung cancer by administering paclitaxel or carboplatin in combination with the cytokine inducer [R-(R*,R*)]-N-[(R)-6-carboxy-N2-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]-ethoxy]carbonyl]-L-lysyl]-alanine, does not reasonably provide enablement for the treatment of solid tumors of all types by administering the same, nor does it reasonably provide enablement for co-administration of the cytokine inducer *supra* with any chemotherapeutic agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;
2) the breadth of the claims;
3) the predictability or unpredictability of the art;
4) the amount of direction or guidance presented;
5) the presence or absence of working examples;
6) the quantity of experimentation necessary;
7) the state of the prior art; and,
8) the relative skill of those skilled in the art.

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

The presently clamed invention is directed to a method for treating a solid tumor in a mammal which comprises administering to said mammal an effective amount of a combination comprising a cytokine inducer and a chemotherapeutic agent, wherein the cytokine inducer is [R-(R*,R*)]-N-[(R)-6-

carboxy-N2-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]-ethoxy]carbonyl]-L-lysyl]-alanine. The claims additionally specify that the chemotherapeutic agent may be a microtubular agent or macrophage activating agent, such as, e.g., paclitaxel, docetaxel, vincristine, vinblastine, vinorelbine, doxorubicin, cisplatin, carboplatin, mitomycin C or bleomycin (claims 16-18).

In particular, one skilled in the art could not practice the presently claimed subject matter without undue experimentation because the artisan would not accept on its face that the treatment of any solid tumor could be effectively achieved by the administration of the claimed cytokine inducer co-administered with any chemotherapeutic agent other than paclitaxel or carboplatin. Based upon the state of the art, as discussed below, the artisan would have only accepted that the treatment of specific tumor types could be achieved with this combination of compounds identified as having activity in treating such tumor types.

As set forth in *In re Marzocchi et al.*, 169 USPQ 367 (CCPA 1971):

"[A] [s]pecification disclosure which contains the teachings of manner and process of making and using the invention in terms corresponding to the scope to those used in describing and defining subject matter sought to be patented must be taken as in compliance with the enabling requirement of first paragraph of 35 U.S.C. 112 *unless there is reason to doubt the objective truth of statements contained therein which must be relied on for enabling support*; assuming that sufficient reasons for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis, such a rejection can be overcome by suitable proofs indicating that teaching contained in the specification is truly enabling." (emphasis added)

The present claims circumscribe a method for treating any type of solid tumor by administering the claimed combination of a chemotherapeutic agent with the cytokine inducer [R-(R*,R*)]-N-[(R)-6-carboxy-N2-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]-ethoxy]carbonyl]-L-lysyl]-alanine. That is, in order to be enabled to practice the present invention, the skilled artisan would have to accept that by

administering the presently claimed combination, all solid tumors, including non-small cell lung cancer, known in the art could be treated. In light of the fact that the specification not only fails to provide the skilled artisan with any direction or guidance as to how the treatment of any solid tumor type, aside from non-small cell lung cancer, could actually be achieved using the claimed combination of agents, but also fails to direct the skilled artisan as to which other tumor types would be sensitive to this chemotherapeutic combination, which chemotherapeutic agents could be reasonably employed to produce an anticancer effect when used in the claimed combination and how one would determine such sensitivity without requiring a need for undue experimentation, the specification, which lacks an objective showing of which other solid tumors could be effectively treated using the claimed combination, is viewed as lacking an enabling disclosure of the entire scope of the claimed invention, especially in light of the highly complex nature of tumors and cancer in general.

Here, the objective truth that any solid tumor type may be treated with the claimed combination of agents is doubted because, while the state of the art of cancer treatment is well developed with regard to the treatment of specific cancer types with specific chemotherapeutic regimens (see Cecil's Textbook of Medicine, pages 1060-1074), the state of the art with regard to treating all tumors, even all solid tumors, using a single agent or single combination of agents is grossly underdeveloped.

In this regard, Cecil's Textbook of Medicine (2000) is cited. In particular, there is no known anticancer agent or combination of anticancer agents that is effective against treating all cancer types, or even all solid tumor types, nor is there any known anticancer agent or combination of agents that is effective against inhibiting the growth of any type of cancer cell. The Cecil reference clearly shows that for the various known cancer types, there is not one specific chemotherapeutic agent or combination thereof that is effective at treating cancer or inhibiting the growth of cancer cells for each and every type of cancer (see Table 198-5 at page 1065; Tables 198-6 and 198-7 at pages 1066; Table 198-8 at page 1068; and Table 198-9 at page 1071).

Given that there was not known any specific agent or combination of agents effective to treat all known tumor types or even all solid tumor types, one of ordinary skill in the art would not accept on its face Applicant's statement that such an objective could be achieved in any type of solid tumor using the presently claimed combination of agents without enabling a set of species representative of the full scope of solid tumors known in the art. The artisan would have required sufficient direction as to how, at minimum, a representative set of species of solid tumors could be effectively treated with the claimed combination of compounds and, further, how the artisan could have reasonably extrapolated such results to the larger and highly varied genus of solid tumors in general without requiring undue experimentation to determine what other types of solid tumor would actually show sensitivity to the presently claimed combination, such that the artisan would have been imbued with at least a reasonable expectation of success in treating the cancer. Such success would not have been reasonably expected for all solid tumors claimed given the highly complex and variable nature of all cancers known in the art and that Applicant has shown a single example in non-small cell lung cancer cells. To the artisan, the concept of a single agent or a single combination of agents effective to treat this single solid tumor types would not have been considered representative or suggestive of the same efficacy in the treatment of all known types of solid tumors in the absence of any evidence or reasoning to do so. Additionally, since the skilled artisan would have expected the interaction of a particular agent in the treatment of a particular disease state to be very specific and highly unpredictable absent a clear understanding of the structural and biochemical basis for the use of each agent, one of skill in the art would have no other recourse but undue experimentation to undertake extensive testing to determine which other solid tumor types would be amenable to treatment using the claimed combination of agents.

It is in this regard that Applicant is directed to the MPEP at §2164.08. All questions of enablement are evaluated against the claimed subject matter. Concerning the breadth of a claim relevant to enablement, the only relevant concern is whether the scope of enablement provided to one skilled in the

art by the disclosure is commensurate with the scope of protection sought by the claims. The determination of the propriety of a rejection based upon the scope of a claim relative to the scope of enablement involves the determination of how broad the claim is with respect to the disclosure and the determination of whether one skilled in the art is enabled to use the *entire scope* of the claimed invention without undue experimentation.

A conclusion of a lack of enablement must take into consideration the unpredictability in the art at the time of the invention and the direction or guidance provided by Applicant. The amount of guidance required to be present in the specification as originally filed is directly proportional to the amount of knowledge in the art as well as the unpredictability in the art. In other words, if little or nothing is known in the prior art about an aspect of the claimed invention and the art is unpredictable, the specification needs more detail and guidance as to how to use the invention in order to be enabling. Please reference *In re Fisher*, 417 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) and *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004).

The enablement of the working example provided in the specification is not disputed. However, it is not representative of the breadth of the presently claimed subject matter. Applicant's claims broadly claim the use of the any chemotherapeutic agent in combination with [R-(R*,R*)]-N-[(R)-6-carboxy-N2-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]-ethoxy]carbonyl]-L-lysyl]-alanine for use in treating *any solid tumor*. The fact that Applicant has exemplified the use of this compound in non-small cell lung cancer cells alone does not address the high degree of variability in the art in terms of the pathophysiological differences among solid tumor types and their reactivity to different anticancer compounds. Applicant has also failed to provide any evidence, or describe any protocol, that addresses this variability in the art such that one of ordinary skill in the art would have been imbued with at least a reasonable expectation of success in treating any solid tumor with the claimed combination based on the direction provided in the present specification. While the lack of a working embodiment cannot be the

sole factor in determining enablement, the absence of substantial evidence commensurate in scope with the presently claimed subject matter, in light of the unpredictable nature of the art and the direction that Applicant has presented, provides additional weight to the present conclusion of insufficient enablement in consideration of the *Wands* factors as a whole.

For example, the term "solid tumor" alone encompasses three distinctly different categories of tumors: (1) sarcomas, those that arise from connective or supporting tissues, such as bone or muscle; (2) carcinomas, those that arise from glandular tissues and epithelial cells; and (3) lymphomas, those that arise from the lymphoid organs, such as the lymph nodes, spleen or thymus. Though each of these three types can be lumped under the umbrella category of "solid tumor", the distinct etiology and pathophysiological differences between these three categories of solid tumor would not have imbued the skilled artisan with a reasonable expectation of success in treating any one or more of these types of solid tumor when efficacy had only been demonstrated in a single cancer cell type (i.e., non-small cell lung).

In light of such, it is clear that one of ordinary skill in the art would be faced with the impermissible burden of undue experimentation in order to execute the entire scope of the subject matter presently claimed. The basis for the present rejection is not simply that experimentation would be required, since it is clear from the state of the pharmaceutical and chemical arts that experimentation in this particular art is not at all uncommon, but that the level of experimentation required in order to practice this aspect of the invention in the absence of any enabling direction by Applicant would be *undue*. Please reference *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976), which states, "The test of enablement is not whether any experimentation is necessary, but whether, *if experimentation is necessary, it is undue*." (emphasis added) Given the high degree of unpredictability noted and recognized in the art with regard to the treatment of cancer and tumors, the state of the art clearly precludes the general extrapolation of the results exemplified to the larger and much more highly varied genus of cancers and tumors as a whole. In the absence of any direction or guidance presented by

Applicant as to how such a therapeutic objective could be achieved without necessitating an undue level of experimentation, the present disclosure is viewed as lacking an enabling disclosure of the *entire scope* of the presently claimed subject matter.

In view of the discussion of each of the preceding seven factors, the level of skill in the art is high and is at least that of a medical doctor with several years of experience in the art.

As the cited art and discussion of the above factors establish, practicing the claimed method in the manner disclosed by Applicant would not imbue the skilled artisan with a reasonable expectation that the use of the claimed combination of any chemotherapeutic agent with the cytokine inducer [R-(R*,R*)]-N-[(R)-6-carboxy-N2-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]-ethoxy]carbonyl]-L-lysyl]-alanine would have necessarily had efficacy in the treatment of any solid tumor type. In order to actually achieve such a result, it is clear from the discussion above that the skilled artisan could not rely upon Applicant's disclosure as required by 35 U.S.C. 112, first paragraph, and would have no alternative recourse but the impermissible burden of undue experimentation in order to practice the full scope of the presently claimed invention.

Claim Rejections - 35 USC § 103 (New Grounds of Rejection)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

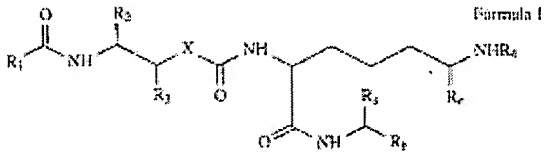
This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of

each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Francis et al. ("Paclitaxel (Taxol) and Docetaxel (Taxotere): Active Chemotherapeutic Agents in Lung Cancer", *Lung Cancer*, 1995, 12 Suppl.1:S163-S172) in view of Ayral-Kaloustian et al. (U.S. Patent No. 5,545,662; 1996).

Francis et al. is cited for its teaching that paclitaxel and docetaxel are among the most active chemotherapeutic agents for non-small cell lung cancer patients (abstract). Francis et al. teaches that the dose-limiting toxicity for both paclitaxel and docetaxel in Phase I studies in lung cancer patients was neutropenia (Sect. 3, p.S166) and further teaches that neutropenia was also the most common toxicity observed in Phase II clinical trials of each of paclitaxel or docetaxel in advanced non-small cell lung cancer patients (Sect. 4, p.S166-S167).

The difference between Francis et al. and the instant claims lies in the fact that Francis et al. fails to teach concomitant use of the claimed cytokine inducer compound, [R-(R*,R*)]-N-[(R)-6-carboxy-N2-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy]carbonyl]-L-lysyl]-D-alanine, with the paclitaxel or docetaxel therapy for treating non-small cell lung cancer.

However, Aryal-Kaloustian et al. is cited for its teaching of urea and urethane compounds of the formula  or pharmaceutically acceptable salts thereof (col.2, l.41-42), of which the specific compound [R-(R*,R*)]-N-[(R)-6-carboxy-N2-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy]carbonyl]-L-lysyl]-D-alanine is exemplified (Ex.28, col.31, l.1-20), for use in restoring neutrophils after cancer chemotherapy by inducing endogenous production of IL-6 and GCSF

growth factors, each of which are known to regulate neutrophil production in the bone marrow (col.19, l.18-31; see also Tables 1-3 at cols.19-20). In fact, Aryal-Kaloustian et al. expressly teaches a study of the compound of Example 28 (identical to Applicant's claimed cytokine inducer; see col.31, l.1-20), which demonstrated synergistic activity *in vitro* with c-kit ligand in enhancing the growth of bone marrow progenitor cells, which was understood to support the claim that this compound acted to enhance the growth of neutrophil progenitor cells in the bone marrow (col.19, l.5-15).

In view of such teachings, one of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to use the urea compound(s) of Aryal-Kaloustian et al., particularly the compound of Example 28 (i.e., [R-(R*,R*)]-N-[(R)-6-carboxy-N2-[[2-carboxy-1-methyl-2-[(1-oxoheptyl)amino]ethoxy]carbonyl]-L-lysyl]-D-alanine; identical to Applicant's claimed cytokine inducer compound of claim 15), in combination with the paclitaxel or docetaxel treatment of advanced non-small cell lung cancer (i.e., a "solid tumor" as instantly claimed in claim 15), to provide neutrophil rescue and enhanced neutrophil production to overcome the common neutropenic toxicity associated with such treatments in NSCLC patients, as evidenced by the studies of this compound presented in Aryal-Kaloustian et al. The artisan would have been clearly motivated to do so to ameliorate the dose-limiting neutropenia toxicity in NSCLC patients treated with paclitaxel or docetaxel by restoring neutrophil generation in the bone marrow via the production of IL-6 and GCSF, each of which stimulates neutrophil generation in the bone marrow and, thus, would have been reasonably expected to restore normal neutrophil function and eliminate neutropenic toxicity in such patients.

Conclusion

Rejection of claims 15-18 is proper and is **maintained**.

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Leslie A. Royds
Patent Examiner
Art Unit 1614

October 5, 2007

10/7/07
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SUPERVISORY PATENT EXAMINER